1: Allergy. 1997;52(34 Suppl):44-7.

The eosinophil and the eye.

Bonini S, Magrini L, Rotiroti G, Lambiase A, Tomassini M, Rumi C, Bonini S.

Second University of Naples, Italy.

Personal studies in allergic eye diseases reviewed in this paper indicate that: 1. An increased number and an abnormal distribution of eosinophils is present in conjunctival biopsies of patients with vernal keratoconjunctivitis (VKC). 2. Eosinophil and eosinophil products, such as ECP, are also increased in tears of VKC patients and, in hay fever conjunctivitis, accumulate during the late-phase of allergic reaction following specific allergen challenge. 3. Circulating eosinophils of VKC patients show a typical activation phenotypic profile which is associated with increased serum level of eosinophil cationic protein and eosinophil-derived neurotoxin/protein X. A clinical study of the modulatory effect of cetirizine on the early and late phase of the allergic reaction as well as on the eosinophil activation and tissue recruitment following conjunctival allergen challenge is reported as an example of the need to evaluate eosinophil functions when investigating anti-allergic drugs. Drugs modulating various aspects of eosinophil function could play a primary role in the treatment of allergic eye disease.

Publication Types:

- Review
- Review, Tutorial

PMID: 9188953 [PubMed - indexed for MEDLINE]

1: J Appl Physiol. 1999 Feb;86(2):659-68.

Relationship between histamine and physiological changes during the early response to nasal antigen provocation.

Baroody FM, Ford S, Proud D, Kagey-Sobotka A, Lichtenstein L, Naclerio RM.

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To investigate the temporal relationships of mediator release and physiological changes during the early response to allergen, we challenged allergic individuals intranasally with antigen and followed their responses. This was done by using small filter paper disks to challenge one nostril and collect secretions from both the challenged and the contralateral nostril, thus enabling us to evaluate the nasonasal reflex. There was a significant increase in sneezing after allergen challenge that peaked within 2 min and returned to baseline. The weights of nasal secretions as well as nasal symptoms increased immediately and remained significantly elevated for 20 min in both nostrils. Nasal airway resistance increased slowly, reaching its peak at approximately 6 min after challenge on the ipsilateral side, but it did not change on the contralateral side. Histamine levels peaked 30 s after removal of the allergen disk on the side of challenge, whereas albumin levels peaked after those of histamine. Lactoferrin paralleled the increase in secretion weights and occurred in both nostrils. Increasing doses of antigen produced dose-dependent increases in all parameters, whereas control challenges produced no response. These studies describe a human model for the evaluation of the allergic response that is capable of simultaneously measuring mediator release and the physiological response, including the nasonasal reflex. This model should prove useful in studying the mechanism of allergic rhinitis in humans.

Publication Types:
- Clinical Trial

PMID: 9931205 [PubMed - indexed for MEDLINE]

1: Clin Exp Allergy. 1998 Dec;28 Suppl 6:20-4.

The inflammatory nature of allergic disease.

Durham SR.

Allergy and Clinical Immunology, National Heart and Lung Institute, London, UK.

The allergic inflammatory response in allergic rhinitis has been studied extensively owing to the high frequency of the condition, the significant morbidity it causes and the accessibility of the nasal tissue. The allergic inflammatory response is characterized by IgE synthesis, IgE-dependent mast cell activation and infiltration of the nasal mucosa by T lymphocytes and eosinophils. The immediate-phase response is mediated by a range of inflammatory mediators (such as histamine, leukotrienes and prostaglandins), resulting in vasodilatation, oedema, mucus secretion, itching and sneezing. Individuals who experience a late-phase response have further nasal symptoms 4-24 h after the initial challenge with allergen. Results of nasal biopsy studies indicate that the late-phase allergic response involves T-lymphocyte activation, production of TH2-type cytokines and tissue eosinophilia. Corticosteroids potently inhibit T-lymphocyte responses, and clinical studies in subjects with allergic rhinitis have demonstrated that they are extremely effective in blocking both early- and late-phase allergic reactions. Topical aqueous triamcinolone acetonide nasal spray represents a novel formulation of a topical corticosteroid for the treatment of allergic rhinitis. Data from controlled clinical studies indicate that it is effective in treating seasonal and perennial disease, is well tolerated, does not suppress adrenocortical function, is odourless, and can be administered as a once-daily dose.

Publication Types:

- Review
- Review, Tutorial

PMID: 9988430 [PubMed - indexed for MEDLINE]

1: Int Arch Allergy Immunol. 1997 Sep;114(1):68-73. Related Articles, Links

Inhibition of allergen-induced histamine release from human basophils by cyclosporine A and FK-506.

Sperr WR, Agis H, Semper H, Valenta R, Susani M, Sperr M, Willheim M, Scheiner O, Liehl E, Lechner K, Valent P.

Department of Internal Medicine I, University of Vienna, Austria.

A number of structurally different allergens trigger the release of mediators from basophils by cross-linking of IgE receptors. In this study, we analyzed the effects of cyclosporine A (CSA) and FK-506 on allergen-induced histamine release in human blood basophils obtained from birch- or grass-pollen-allergic donors (n = 12). Preincubation of basophils with CSA (0.003-3 microg/ml) or FK-506 (0.003-3 microg/ml) led to inhibition of histamine release induced by purified recombinant tree pollen allergens (r Bet v 1, r Bet v 2) and timothy grass pollen allergens (r Phl p 1, r Phl p 2, r Phl p 5). The effects of CSA and FK-506 were dose dependent, with IC50 values ranging between 0.03 and 0.3 microg/ml for both CSA and FK-506. Cyclosporine H, an inactive CSA analog, did not show any effect on allergen-induced histamine secretion. IgE dependency of the reaction was demonstrated in passive transfer experiments using highly enriched human basophils (> 95% pure) and specific IgE from a patient allergic to Bet v 2. In summary, our data show that CSA and FK-506 inhibit recombinant-allergen-induced histamine release from peripheral blood basophils in allergic donors.

PMID: 9303333 [PubMed - indexed for MEDLINE]

1: Ophthalmologe. 1998 Apr;95(4):241-6.

[Histamine in tears in allergic rhinoconjunctivitis]

[Article in German]

Struck HG, Wicht A, Ponicke K, Lautenschlager C, Lubbe D.

Klinik und Poliklinik fur Augenheilkunde, Martin-Luther-Universitat, Halle-Wittenberg.

The classic clinical symptoms of allergic conjunctivitis (type I allergy)--itching and lacrimation--are the effect of histamine. Determination of histamine levels in tears may be useful in evaluating the dynamics of local histamine release in connection with the clinical findings. PATIENTS AND METHODS: Between 1.7.1994 and 31.6.1995 we analyzed the histamine levels in tears and investigated the clinical symptoms (score of 0-3) of 32 hyposensitized pollen-sensitive patients (14 males and 18 females, aged 18-45 years, group I) and of 32 controls (group II) without any allergic disease, performed in each case once in season and once out of season. Tear production and composition were measured by Schirmer's test and tear break-up time at the same time. The histamine levels of the tear samples (obtained by microcapillary method) were analyzed by electrochemical determination. RESULTS: In group I there was a highly significant increase of the mean histamine level from 0.89 +/- 2.22 ng/ml (out of season) to 7.71 +/- 7.51 ng/ml (in season) for the right eye and from 0.73 +/- 2.36 ng/ml (out of season) to 9.51 +/- 9.07 ng/ml (in season) for the left eye (P = 0.0000). The histamine level in tears of the controls (group II) was below the detection limit in all samples. The seasonal histamine level were higher with the severity of atopy (Erlangen atopy score). There was no significant influence of age and gender. The reduction of allergic symptoms during hyposensitization was not comparable to the degree of seasonal histamine level. Compared with the clinical findings, the histamine level in tears did not correlate with the symptoms of lacrimation, itching and conjunctival hyperemia. CONCLUSION: The histamine level in tears alone is not useful as a marker for the clinical severity of this atopyassociated disorder and for the efficacy of the anti-allergic therapy. After standardization of the determination method and the identification of other soluble mediators simultaneously, the histamine level in tears can be used as one part of a profile of mediators to evaluate the clinical symptoms.

1: Acta Ophthalmol Scand Suppl. 1999;(228):33-7. Related Articles, Links

A current appreciation of sites for pharmacological intervention in allergic conjunctivitis: effects of new topical ocular drugs.

Yanni JM, Sharif NA, Gamache DA, Miller ST, Weimer LK, Spellman JM.

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Two important realizations about pathophysiological mechanisms involved in allergic conjunctivitis have led to novel drug discovery efforts and new topical ocular medications for prevention and treatment of this prevent allergic disease. The first of these, interspecies and intraspecies mast cell heterogeneity, was established in the mid-1980's by investigators working in the field of asthma. It is now appreciated that secretory responses as well as effects of pharmacological agents differ depending upon the mast cell population studied. Two types of human mast cells, the tryptase containing (T) and the tryptase/chymase containing (TC) mast cells, have been characterized in a variety of tissues. Significantly, Irani et al. (1) demonstrated by immunohistochemical staining that the mast cells present in conjunctival tissues from patients with allergic conjunctivitis were 100% TC. Functional responses of human conjunctival mast cells to a variety of secretagogues (2) were consistent with their classification as TC or connective tissue type mast cells. Importantly, the studies by Miller et al. mentioned above allowed the harvesting and preparation of human conjunctival mast cells for use in drug screening studies. Utilization of these cells has led to the identification of Patanol, the most effective human conjunctival mast cell stabilizer available for topical use in allergic conjunctivitis (3). These same studies demonstrated the lack of mast cell stabilizing activity for cromolyn and nedocromil in these connective tissue type, TC containing, human conjunctival mast cells. Similar lack of effect was noted with these drugs on human skin mast cell degranulation (4). The second important discovery in the area of allergic conjunctivitis has been the demonstration that conjunctival epithelial cells may contribute to the perpetuation of the allergic response. A report from Gamache et al. (5) identified cytokines produced by human conjunctival epithelial cells following treatment with a number of stimuli. Significantly, Sharif et al. (6) subsequently identified functional histamine H1 receptors on these same cell types.

Recently, Weimer et al. (7) have shown that exposure of human conjunctival epithelial cells to histamine leads to the production of pro-inflammatory cytokines IL-6 and IL-8. Importantly, treatment of the epithelial cells with drugs that possess histamine H1 antagonist properties prevents cytokine production. It is noteworthy that first generation anti-histamines antazoline and pheniramine are not potent inhibitors of histamine-stimulated cytokine synthesis in intact epithelial cells, while newer anti-histamines Emadine and levocabastine are more potent. Surprisingly, Patanol was more potent as an inhibitor of histamine-stimulated cytokine production by the epithelial cells than would be predicted from its histamine H1 antagonist affinity. These inhibitory effects on conjunctival epithelial cell production of pro-inflammatory cytokines may contribute to enhanced clinical activity noted with these recently approved drugs.

Publication Types:

- Review
- Review, Tutorial

PMID: 10337430 [PubMed - indexed for MEDLINE]

All: 1 Review: 0

1: Int Arch Allergy Immunol. 1998 Apr;115(4):288-93. Related Articles, Links

Full Text

Histamine-stimulated cytokine secretion from human conjunctival epithelial cells: inhibition by the histamine H1 antagonist emedastine.

Weimer LK, Gamache DA, Yanni JM.

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The present studies demonstrate that histamine induces the secretion of IL-6, IL-8 and GM-CSF from human conjunctival epithelial cells in a dose- and time-dependent manner. The histamine antagonists emedastine (H1), ranitidine (H2) and thioperamide (H3) were evaluated for their ability to inhibit secretion of these cytokines. Emedastine potently inhibited histamine-induced IL-6, IL-8 and GM-CSF secretion with mean IC50 values of 2.23, 3.42 and 1.50 nM, respectively. Ranitidine and thioperamide failed to inhibit cytokine secretion over a wide dose range. These data suggest that mast cell derived histamine may stimulate inflammatory cytokine production in allergic conjunctivitis via activation of epithelial cell H1 receptors. The histamine H1 antagonist emedastine potently inhibits this response.

PMID: 9566351 [PubMed - indexed for MEDLINE]

1: Wien Med Wochenschr. 1999;149(14-15):415-20. Related Articles, Links

[Theories on the mode of action of desensitization]

[Article in German]

Klimek L, Reske-Kunz AB, Saloga J.

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Specific immunotherapy (SIT) has been practised successfully for about 80 years. In classic immunotherapy, an allergen-extract is repeatedly injected subcutaneously in increasing doses. A large number of clinically controlled studies have proved the efficacy of this kind of immunotherapy, while its mode of action is not precisely known yet. A successful SIT leads to an impairment of allergic symptoms (symptom score), and a concordant decrease in drug use. Furthermore, a reduced reactivity in specific dermal, nasal and bronchial provocation tests is induced as well as a diminished unspecific reagibility in the affected tissues. Several studies showed reduced values for allergen-specific IgE (serum) that followed an initial increase. A reduced immigration of eosinophils was found, both after provocation with allergen and during the pollen season, as well as diminished values of markers for the activity of eosinophils, e.g. eosinophil cationic protein (ECP). Also, a reduced allergen-induced histamine-liberation from mast cells and basophils has been reported. The underlying mechanism for these effects of SIT might be a reorientation of the allergen-induced lymphokine-production to a dominant TH1-cytokine-profile. Because the relation between the quantity of IL-4 and its regulator IFN-gamma controls the extent of IgE-synthesis by B-cells, the reorientation leads to a diminished production of IgE. IFN-gamma inhibits the differentiation of TH2-cells; by this less TH2-cells are present to help B-cells to produce IgE-antibodies, and to induce the differentiation of mast cells and basophils as well as immigration, differentiation and activation of eosinophils. Thus, the positive effects of SIT can be explained by the reorientation T-cell lymphokine profile. The mechanism under discussion for explaining this reorientation include: 1) an increased differentiation of allergen-specific CD4+ precursor-cells or a reorientation of established TH2-cells to the production of IFN-gamma, 2) the differentiation of IFN-gamma-producing CD8+ T-cells and of T-cells with receptors for T-cell-antigenes of the gamma, delta-type; and 3)

All: 1 Review: 1

1: Ann Allergy Asthma Immunol. 1999 Mar;82(3):253-6.

Markedly high eosinophilia and an elevated serum IL-5 level in an infant with cow milk allergy.

Matsumoto T, Goto Y, Miike T.

Department of Child Development, Kumamoto University, School of Medicine, Kumamoto Regional Medical Center, Japan.

BACKGROUND: Interleukin-5 (IL-5) promotes the production and function of eosinophils, and an increase in the serum soluble CD23 (sCD23) level is suggestive of enhanced type-2 helper T-cell activity. The secretion of a large amount of the proinflammatory cytokine, tumor necrosis factor alpha (TNF-a), has been reported to alter the intestinal barrier capacity. OBJECTIVE: To determine whether or not distinct profiles of cytokine production were involved in the marked peripheral eosinophilia of as high as 20,000/mm3 and the gastrointestinal symptoms seen in an infant with cow milk allergy. METHODS: The levels of IL-5, sCD23, and TNF-alpha in serum and the culture supernatants of mononuclear cells were compared with those in infants with anaphylaxis to cow milk and nonallergic infants. RESULTS: Interleukin-5 was detected in the serum (19 pg/mL) but became undetectable after 2 weeks on a milk-free diet together with clinical remission. A kinetic decrease in the serum sCD23 level was also observed during the administration of a milk-free diet with improvement of the eosinophilia in 2 months. The TNF-alpha produced in vitro after stimulation with cow milk protein was not different from in controls. CONCLUSION: It seems likely that the allergic inflammation due to cow milk can induce marked eosinophilia with an associated increase in IL-5 production.

Publication Types:

- Case Reports
- Review
- Review of Reported Cases

PMID: 10094215 [PubMed - indexed for MEDLINE]

1: J Gastroenterol Hepatol. 1998 Oct;13(10):980-9.

Mast cells: a possible link between psychological stress, enteric infection, food allergy and gut hypersensitivity in the irritable bowel syndrome.

Gui XY.

University of Sydney Department of Medicine, Royal North Shore Hospital, St Leonards, New South Wales, Australia.

Intestinal mast cell activation (degranulation), which results from previous enteric infection and/or intestinal allergy, may play a central role in the gut hypersensitivity in both motor response and visceral perception in the Irritable Bowel syndrome. This occurs through various mediators acting on enteric neurons and smooth muscle cells. Psychological stress may trigger this sensitive alarm system via the brain-gut axis.

Publication Types:

- Review
- Review, Tutorial

PMID: 9835312 [PubMed - indexed for MEDLINE]

1: J Allergy Clin Immunol. 1997 Jan;99(1 Pt 1):94-9. Related Articles, Links

J Allergy Clin Immunol

IgE and mast cell response on intestinal allergen exposure: a murine model to study the onset of food allergy.

van Halteren AG, van der Cammen MJ, Biewenga J, Savelkoul HF, Kraal G.

Department of Cell Biology and Immunology, Vrije Universiteit Amsterdam, The Netherlands.

OBJECTIVE: Allergic reactions to food are characterized by enhanced allergen-specific IgE serum levels and the activation of intestinal mast cells. Here we describe a murine model for the onset of food allergy and the role of cytokines in the regulation of food-induced IgE responses. METHODS: Mice were primed systemically with low doses of alum-precipitated ovalbumin. Subsequent intragastric challenge led to enhanced sensitization. RESULTS: Compared with baseline ovalbumin-specific IgE levels before challenge (0.23 +/- 0.06 optical density [OD] units), ovalbumin-challenged mice showed significantly elevated IgE levels (0.86 +/- 0.23 OD units) after intragastric challenge, which were not observed in control animals (0.29 +/- 0.06 OD units). IgE levels mirrored intestinal mast cell activation, measured by decreased histamine levels in duodenal specimens, in ovalbumin-challenged mice (92.6 +/- 7.9 ng/0.1 gm tissue weight) but not in saline-challenged mice (135.4 +/- 18.3 ng/0.1 gm tissue weight), compared with baseline levels (141.1 +/- 4.1 ng/0.1 gm tissue weight). Changes in IgE and histamine levels after intragastric challenge could be blocked by treating the animals with neutralizing antibodies against IL-4 or IL-10. Although it is generally accepted that ingestion of food allergens leads to a state of immunologic unresponsiveness (i.e., oral tolerance), it is shown here that low-dose systemic priming followed by intragastric challenge leads to sensitization instead of unresponsiveness. CONCLUSIONS: Our murine model shows an important correlation between TH2 cytokines, IgE production, and histamine release. Hence, this in vivo model provides a useful tool with which the complex mechanism underlying sensitization to food allergens can be studied.

PMID: 9003216 [PubMed - indexed for MEDLINE]

1: J Allergy Clin Immunol. 1997 Aug;100(2):216-21.

Related Articles, Links

J Allergy Clin Immunol

Eosinophil cationic protein and histamine after intestinal challenge in patients with cow's milk intolerance.

Bengtsson U, Knutson TW, Knutson L, Dannaeus A, Hallgren R, Ahlstedt S.

Asthma and Allergy Research Center, Sahlgrens' Hospital, Goteborg, Sweden.

BACKGROUND: Mast cells and eosinophils are key cells in the development of active symptoms in allergic diseases and other inflammatory conditions, and they mediate their action through the release of very potent granule constituents. METHODS: Five patients with milk-related gastrointestinal symptoms diagnosed by double-blind placebo-controlled milk challenges, but with negative responses to skin prick tests and RASTs with milk, and eight healthy control subjects were investigated. Repeated perfusion studies were performed with a two-balloon, six-channel tube by using milk, casein, and whey as antigens. Luminal eosinophil cationic protein, histamine, and albumin were measured by radioimmunoassay. RESULTS: Luminal cow's milk induced a pronounced increase in intestinal secretion of histamine and eosinophil cationic protein in patients, but not control subjects, during the first 20 minutes after challenge (histamine from 123 +/- 12 to 543 +/- 175 ng/cm, hr; eosinophil cationic protein from 80 +/- 23 to 686 +/- 262 ng/cm, hr). Albumin, as a marker of plasma leakage, was also significantly increased. CONCLUSION: These data indicate that mast cells and eosinophils are effector cells not only in patients with allergic disease but also in patients intolerant to foods and lacking circulating antibodies. The underlying mechanisms may be a reaction mediated by locally appearing antibodies or an immunologic activation resembling that found in intestinal disorders such as celiac disease.

PMID: 9275143 [PubMed - indexed for MEDLINE]

1: Panminerva Med. 1998 Sep;40(3):186-90. Related Articles, Links

Study of release of eosinophil cationic proteins (ECP and EPX) in the hypereosinophilic syndrome (HES) and other hypereosinophilic conditions.

Bobbio-Pallavicini E, Confalonieri M, Tacconi F, Mainardi E, Della Porta R, Ceccato D, Maccario R, De Amici M.

Division of General Medicine, Ospedale Maggiore, Crema, Italy.

BACKGROUND: Up to date, the etiology and the pathogenesis of HES are still unknown and particularly it is unclear why eosinophils in HES are more aggressive towards tissues than in other eosinophilic conditions. METHODS: We assessed the cationic proteins ECP and EPX serum concentrations, their in vitro release from polymorphonuclear cell culture, and the monoclonal antibodies EG1 and EG2 in 3 patients with HES, 6 patients with other hypereosinophilic conditions and 20 healthy control subjects. RESULTS: Serum ECP and EPX concentrations were higher in eosinophilic patients than in healthy subjects. Hypereosinophilic patients had more EG2+ cells than healthy subjects, but EG2+ rate failed to differentiate HES from other hypereosinophilic conditions ($p = 0.074$). Moreover, the release in vitro of ECP and EPX was significantly higher in HES patients ($p < 0.05$). CONCLUSIONS: Our preliminary results seem to suggest the importance of functional data, such as ECP and EPX release, in differentiating HES from other hypereosinophilic diseases. Particularly, ECP and EPX release in vitro is higher in cell cultures from HES patients than from patients with other hypereosinophilic conditions.

PMID: 9785914 [PubMed - indexed for MEDLINE]

1: Dermatology. 1999;199(1):35-9.

The ultrastructural patterns of mast cell degranulation in Kimura's disease.

Aoki M, Kawana S.

Department of Dermatology, Nippon Medical School Main Hospital, Tokyo, Japan.

BACKGROUND: Although Kimura's disease has been considered an atopic disease because of the association of peripheral blood eosinophilia and elevated serum IgE, the mechanisms of these phenomena are still unknown. OBJECTIVE: It is now established that mast cells are a source of cytokines that are involved in eosinophil recruitment or IgE production. In order to understand the role of mast cells in Kimura's disease, we conducted ultrastructural studies. METHOD: The 45 mast cells obtained from 2 patients with Kimura's disease were classified into two subgroups: S type, with a predominance of scroll or crystal subelements in their granules, and P type, predominantly possessing a particulate or filamentous substructure. RESULTS: We observed numerous P type mast cells with focal losses of granule contents in the absence of granule extrusion in Kimura's disease. CONCLUSION: These results indicate the possibility that slow release of mediators or cytokines from mast cells by piecemeal degranulation may contribute to the pathomechanism of Kimura's disease.

Publication Types:
- Case Reports

PMID: 10449955 [PubMed - indexed for MEDLINE]

1: Clin Sci (Lond). 1999 Apr;96(4):349-55.

Clinical Science

Adenosine induces histamine release from human bronchoalveolar lavage mast cells.

Forsythe P, McGarvey LP, Heaney LG, MacMahon J, Ennis M.

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Previous studies have shown that in vitro adenosine enhances histamine release from activated human lung mast cells obtained by enzymic dispersion of lung parenchyma. However, adenosine alone has no effect on histamine release from these cells. Given the evidence for direct activation of mast cells after endobronchial challenge with adenosine and previous studies indicating that mast cells obtained at bronchoalveolar lavage are a better model for asthma studies than those obtained by enzymic dispersion of lung tissue, the histamine-releasing effect of adenosine was examined on lavage mast cells. Bronchoalveolar lavage fluid was obtained from patients attending hospital for routine bronchoscopy (n=54). Lavage cells were challenged with adenosine or adenosine receptor agonists (20 min, 37 degrees C) and histamine release determined using an automated fluorometric assay. Endogenous adenosine levels were also measured in lavage fluid (n=9) via an HPLC method. Adenosine alone caused histamine release from lavage mast cells in 37 of 54 patients with a maximal histamine release of 20.56+/-2.52% (range 5.2-61%). The adenosine receptor agonists (R)-N6-(2-phenylisopropyl)adenosine, 5'-N-ethylcarboxamidoadenosine and CGS21680 also induced histamine release from lavage mast cells. Preincubation of lavage mast cells with the adenosine receptor antagonist xanthine amine congener caused significant inhibition of the response to adenosine (P=0.007). There was an inverse correlation between endogenous adenosine levels in the lavage fluid and the maximal response to in vitro adenosine challenge of the lavage cells. The findings of the present study indicate a means by which adenosine challenge of the airways can induce bronchoconstriction and support a role for adenosine in the pathophysiology of asthma. The results also suggest that cells obtained from bronchoalveolar lavage fluid may provide the ideal model for the testing of novel, adenosine receptor, targeted therapies for asthma.

PMID: 10087241 [PubMed - indexed for MEDLINE]

1: Clin Exp Allergy. 1999 Apr;29(4):543-9.

Enhanced basophil histamine release and neutrophil chemotactic activity predispose grain dust-induced airway obstruction.

Park H, Jung K, Kang K, Nahm D, Cho S, Kim Y.

Department of Allergy and Clinical Immunology, Ajou University School of Medicine, Suwon, Korea.

BACKGROUND: The pathogenic mechanism of grain dust (GD)-induced occupational asthma (OA) remains unclear. OBJECTIVE: To understand further the mechanism of GD-induced OA. METHODS: Fifteen employees working in a same GD industry, complaining of work-related respiratory symptoms, were enrolled and were divided into two groups according to the GD-bronchoprovocation test (BPT) result: six positive responders were grouped as group III, nine negative responders as group II and five healthy controls as group I. Serum GD-specific immunoglobulin (Ig)E (sIgE), specific IgG (sIgG) and specific IgG4 (sIgG4) antibodies were detected by enzyme-linked immunosorbent assay. Basophil histamine release was measured by the autofluorometric method, and changes of serum neutrophil chemotactic activity were observed by the Boyden chamber method. RESULTS: For clinical parameters such as degree of airway hyperresponsiveness to methacholine, duration of respiratory symptoms, exposure duration, and prevalences of serum sIgE, sIgG and sIgG4 antibodies, there were no significant differences between group II and III ($P > 0.05$, respectively). Serum neutrophil chemotactic activity increased significantly at 30 min and decreased at 240 min after the GD-BPT in group III subjects ($P < 0.05$, respectively), while no significant changes were noted in group II subjects ($P > 0.05$). Basophil histamine release induced by GD was significantly higher in group III than those of group I or group II ($P < 0.05$, respectively), while minimal release of anti-IgG4 antibodies was noted in all three groups. CONCLUSIONS: These results suggest that enhanced basophil histamine release and serum neutrophil chemotactic activity might contribute to the development of GD-induced occupational asthma.

PMID: 10202370 [PubMed - indexed for MEDLINE]

1: Ann Rheum Dis. 1999 May;58(5):297-302.

Macrophage inflammatory protein 1 alpha expression by synovial fluid neutrophils in rheumatoid arthritis.

Hatano Y, Kasama T, Iwabuchi H, Hanaoka R, Takeuchi HT, Jing L, Mori Y, Kobayashi K, Negishi M, Ide H, Adachi M.

The First Department of Internal Medicine, Showa University School of Medicine, Tokyo, Japan.

OBJECTIVE: To determine the contribution made by synovial fluid (SF) neutrophils to the augmented expression of macrophage inflammatory protein 1 alpha (MIP-1alpha) in rheumatoid arthritis (RA). METHODS: Neutrophils were isolated from samples of SF from RA patients and peripheral blood (PB) samples from RA patients and healthy controls. Cell associated MIP-1alpha was visualised immunohistochemically, and cell associated MIP-1alpha as well as MIP-1alpha secreted into the SF was assayed by ELISA. Steady state expression of MIP-1alpha mRNA was assessed by reverse transcription polymerase chain reaction (RT-PCR). RESULTS: Freshly isolated SF neutrophils contained significantly higher concentrations of both MIP-1alpha protein and its transcript than PB neutrophils from either RA patients or healthy controls; incubation in the absence or presence of tumour necrosis factor alpha for 24 hours resulted in a significant increase in MIP-1alpha secretion by RA SF neutrophils compared with neutrophils obtained from either normal PB or RA PB; and expression of MIP-1alpha by SF neutrophils was well correlated with both RA disease activity and SF mononuclear cell (MNC) counts. CONCLUSION: Expression and secretion of MIP-1alpha by SF neutrophils may be indicative of local and systemic inflammation in RA. Moreover, this C-C chemokine may contribute to the recruitment of MNCs from the bloodstream into synovial joints and tissues.

PMID: 10225815 [PubMed - indexed for MEDLINE]

1: J Immunol. 1999 May 15;162(10):6278-83.

The beta2-adrenergic agonist salbutamol is a potent suppressor of established collagen-induced arthritis: mechanisms of action.

Malfait AM, Malik AS, Marinova-Mutafchieva L, Butler DM, Maini RN, Feldmann M.

Kennedy Institute of Rheumatology, Hammersmith, London, United Kingdom.

The therapeutic potential of salbutamol, a beta2-adrenergic agonist, was explored in collagen-induced arthritis. This study was based on a report that salbutamol, by elevating intracellular cAMP, inhibits IL-12 production by macrophages and dendritic cells, thus preventing Th1 development. Ten-week-old male DBA/1 mice were immunized by intradermal injection of type II collagen in CFA. Arthritis developed 15-30 days later and the mice were treated after onset of disease with salbutamol, 200 microgram i.p. After 10 days, the mice were sacrificed, and the hind paws were evaluated histologically. Salbutamol, 200 microgram daily or every other day, had a profound therapeutic effect on the clinical progression of arthritis, as assessed by clinical score and paw thickness. The therapeutic effect was dose dependent. Daily administration of 200 microgram of salbutamol offered the best protection against joint damage, as assessed by histology. In vitro, salbutamol reduced IL-12 and TNF-alpha release by peritoneal macrophages in a dose-dependent manner, as well as TNF release by synovial cells from arthritic mice. Ex vivo, draining lymph node cells of the salbutamol-treated arthritic mice showed a diminished CII-specific IFN-gamma production and proliferation. In vivo, salbutamol specifically blocked mast cell degranulation in joint tissues. In conclusion, salbutamol has important effects on the immunoinflammatory response and a significant therapeutic action in collagen-induced arthritis.

PMID: 10229875 [PubMed - indexed for MEDLINE]

All: 1 Review: 0

1: Clin Exp Immunol. 1999 Jul;117(1):171-6.

Related Articles, Links

Full text blackwell-synergy.com

Peripheral blood mononuclear cells from patients with rheumatoid arthritis spontaneously secrete vascular endothelial growth factor (VEGF): specific up-regulation by tumour necrosis factor-alpha (TNF-alpha) in synovial fluid.

Bottomley MJ, Webb NJ, Watson CJ, Holt PJ, Freemont AJ, Brenchley PE.

Immunology Research, Manchester Royal Infirmary, Manchester, UK.

This study was designed to investigate VEGF production from peripheral blood mononuclear cells (PBMC) from patients with rheumatoid arthritis (RA) compared with healthy controls and to identify the predominant cellular source in PBMC isolated from RA patients. The regulation of PBMC VEGF production by cytokines and synovial fluid (SF) was studied. PBMC were isolated from RA patients and healthy controls and stimulated with lipopolysaccharide (LPS), IL-1beta, IL-4, IL-6, IL-8, IL-10, TNF-alpha and transforming growth factor-beta (TGF-beta) isoforms for varying time points up to 72 h at 37 degrees C/5% CO2. The effect of SF on VEGF secretion by PBMC was also studied. Supernatant VEGF levels were measured using a flt-1 receptor capture ELISA. RA patients had significantly higher spontaneous production of VEGF compared with controls, and monocytes were identified as the predominant cellular source. RA PBMC VEGF production was up-regulated by TGF-beta isoforms and TNF-alpha and down-regulated by IL-4 and IL-10, with no effect observed with IL-1beta, IL-6 and IL-8. Antibody blocking experiments confirmed that TNF-alpha and not TGF-beta isoforms in SF increased VEGF secretion by RA PBMC. These results emphasize the importance of monocytes as a source of VEGF in the pathophysiology of RA. Several cytokines known to be present in SF can modulate the level of VEGF secretion, but the predominant effect of SF in VEGF up-regulation is shown to be dependent on TNF-alpha.

PMID: 10403932 [PubMed - indexed for MEDLINE]

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1: J Rheumatol. 1997 Mar;24(3):436-41.

The effects of traditional antirheumatic herbal medicines on immune response cells.

Chang DM, Chang WY, Kuo SY, Chang ML.

Rheumatology/Immunology/Allergy, Tri-Service General Hospital, Taipei, Taiwan, ROC.

OBJECTIVE: Clinically, some traditional Chinese herbal medicines have been thought to be effective in treating rheumatic diseases such as rheumatoid arthritis and systemic lupus erythematosus. To examine the mechanism by which such herbal remedies might be effective, we investigated the ability of Tripterygium wilfordii Hook-f (TWHf) and tetrandrine (TTD) to affect human immune responsiveness in vitro. METHODS: We measured the ability of these agents to affect cytokine secretion from monocytes or T cells, prostaglandin E2 (PGE2) secretion from monocytes, IgG production from B cells, and the phagocytosis of bacteria by neutrophils. RESULTS: These studies revealed that both TWHf and TTD significantly inhibited interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-alpha), IL-6, and IL-8 secretion from monocytes, IgG secretion from B cells, and phagocytosis of bacteria by neutrophils; however, only TWHf inhibited IL-2 and IL-4 production from lymphocytes, and PGE2 secretion from monocytes. CONCLUSION: TWHf and TTD exert a powerful suppressive effect on human immune responses. This action might account for their therapeutic effectiveness in rheumatic diseases, and might support broader and more rigorous clinical trials.

PMID: 9058645 [PubMed - indexed for MEDLINE]

1: Ann Rheum Dis. 1995 May;54(5):361-5.

Endothelin-1 release from cultured endothelial cells induced by sera from patients with systemic lupus erythematosus.

Yoshio T, Masuyama J, Mimori A, Takeda A, Minota S, Kano S.

Department of Medicine, Jichi Medical School, Tochigi-ken, Japan.

OBJECTIVES--To clarify the pathophysiological role of endothelin-1 (ET-1) in the vascular injury associated with systemic lupus erythematosus (SLE) by investigating the effect of sera from patients with SLE on ET-1 release from cultured human umbilical vein endothelial cells. METHODS--Confluent monolayers of cultured human umbilical vein endothelial cells were incubated with serum samples (diluted 1:10) from 25 patients with SLE and 16 normal controls for two hours at 37 degrees C and ET-1 concentration in the culture supernatant was measured by enzyme immunoassay. RESULTS--The mean release of ET-1 from endothelial cells in the presence of serum from SLE patients was greater than in the presence of serum from normal controls ($p < 0.005$). ET-1 release from endothelial cells significantly correlated with the titre of IgM anti-endothelial cell antibodies (IgM-AECA) and immune complex concentration in sera from SLE patients ($p < 0.05$ and $p < 0.01$, respectively). After gel chromatography of the serum from an SLE patient, those fractions containing IgM-AECA or immune complex were shown to stimulate ET-1 release from endothelial cells. Heat aggregated IgG also stimulated ET-1 release from endothelial cells in a concentration dependent manner. CONCLUSIONS--IgM-AECA and immune complexes may stimulate ET-1 release from endothelial cells and ET-1 may play an important role in the initiation and development of vascular injury, such as pulmonary hypertension and lupus nephritis, in SLE.

PMID: 7794041 [PubMed - indexed for MEDLINE]

1: Eur J Pediatr. 1997 Dec;156(12):921-4.

In vitro release of eosinophil cationic protein from peripheral eosinophils reflects disease activity in childhood Crohn disease and ulcerative colitis.

Luck W, Becker M, Niggemann B, Wahn U.

Virchow-Klinikum, Children's Hospital, Berlin, Germany.

The aim of this study was to compare in vitro release of eosinophil cationic protein (ECP) from peripheral blood eosinophils during active phases of childhood Crohn disease (CD) and ulcerative colitis with phases of remission. Ten children with CD and nine children with ulcerative colitis were investigated during 55 and 56 clinical visits, respectively. Each patient was investigated during at least one phase of clinically active disease and one phase of remission. Disease activity was assessed by means of the Paediatric Crohn Disease Activity Index (PCDAI) in Crohn disease and according to the clinical activity index of Rachmilewitz in ulcerative colitis. On an intra-individual basis, in vitro ECP release was significantly higher ($P < 0.001$) during active phases of CD and ulcerative colitis than in phases of remission (CD:median: 24.5 microg/l, range 16.0-61.2 versus median: 5.7 microg/l, range 2.0-16.7; ulcerative colitis: 14.8 microg/l, 8.3-39.8 versus 4.9 microg/l, 2.0-9.9). On an inte-individual basis, in CD and ulcerative colitis a strong and highly significant correlation was observed between disease activity indices and in vitro release of ECP from peripheral eosinophils ($r = 0.89$, $P < 0.0001$ and $r = 0.82$, $P < 0.0001$, respectively). CONCLUSION: These results show that in vitro ECP release from peripheral eosinophils reflects disease activity in both CD and ulcerative colitis and therefore can be used as a new appropriate laboratory parameter for assessment of disease activity in chronic inflammatory bowel disease.

PMID: 9453373 [PubMed - indexed for MEDLINE]

1: Eur J Clin Invest. 1998 Feb;28(2):145-50. Related Articles, Links

Comment in:
- Eur J Clin Invest. 1999 Jul;29(7):650-1.

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Antioxidants inhibit the in vitro production of inflammatory cytokines in Crohn's disease and ulcerative colitis.

Reimund JM, Allison AC, Muller CD, Dumont S, Kenney JS, Baumann R, Duclos B, Poindron P.

Centre de Recherches Pharmacologiques, Illkirch-Graffenstaden, France.

BACKGROUND: Modulation of cytokine secretion may be of interest in the treatment of Crohn's disease or ulcerative colitis. METHODS: The effect of three antioxidants - butylated hydroxyanisol, tetrahydropapaveroline and nordihydroguaiaretic acid - on the production of tumour necrosis factor (TNF), interleukin (IL) 1, IL-6 and IL-8 (measured by enzyme-linked immunosorbent assay) by peripheral mononuclear cells and biopsies of inflamed colonic mucosa from inflammatory bowel disease patients were studied. RESULTS: We observed a decrease in IL-1 and IL-6 production by peripheral mononuclear cells from inflammatory bowel disease patients (approximately 50% of control). The three drugs did not decrease IL-6 and IL-8 secretion by colonic biopsies, whereas they did inhibit IL-1 and, to some degree, TNF production. The cytokine-inhibitory effect of antioxidants seems to be more pronounced in ulcerative colitis than in Crohn's disease. CONCLUSION: Our results suggest that the studied antioxidants, or related compounds, may be of interest in inflammatory bowel disease treatment.

PMID: 9541129 [PubMed - indexed for MEDLINE]

1: Ital J Gastroenterol Hepatol. 1998 Jun;30(3):338-44. Related Articles, Links

Current concept of the role of monocytes/macrophages in inflammatory bowel disease--balance of proinflammatory and immunosuppressive mediators.

Lugering N, Kucharzik T, Stoll R, Domschke W.

Department of Medicine B, University of Munster, Germany.

Macrophages are important in providing the first line of intestinal defence against microorganisms or toxins that break the epithelial barrier, by presenting antigen to sensitised T cells and releasing a variety of cytokines and inflammatory mediators. During active states in inflammatory bowel disease, large numbers of monocytes leave the bloodstream and migrate into the inflamed mucosa and submucosa. Phenotypic studies have previously shown the presence of much more marked macrophage heterogeneity in inflammatory bowel disease mucosa than in normal mucosa. In both Crohn's disease and in ulcerative colitis, distinct macrophage populations have been found, being prominent in active disease, but absent from normal mucosa. Studies in our institution have shown that the Ca(2+)-binding proteins MRP8 and MRP14 as well as their heterocomplex MRP8/14 (27E10 epitope) are expressed in the majority of granulocytes and macrophages in active but not inactive inflammatory bowel disease. Furthermore, a strong complex MRP8/14 immunoreactivity was present in epithelial cells of the terminal ileum adjacent to ulcerative and fissuring lesions, while epithelial cells of large bowel tissues were consistently negative. In vitro studies revealed that interleukin-13, interleukin-10 and interleukin-4 strongly suppress secretion of different monocytic proteins. A combination of TH2-cytokines even at suboptimal concentrations significantly suppressed protein secretion, much more than using interleukin-13, interleukin-10 or interleukin-4 at a double concentration alone. Our morphological findings demonstrate the presence of MRP8/14 (27E10 antigen) both in monocytes/macrophages and in epithelial cells in active inflammatory bowel disease. Systemic or topical application of combined cytokine treatment might be a new effective therapeutic approach for chronic inflammatory bowel disease especially in those cases in which monocytes/macrophages lose their ability to respond, to some degree, to anti-inflammatory cytokines.

Publication Types:

1: Scand J Gastroenterol. 1999 May;34(5):496-503. Related Articles, Links

Effect of substance P on histamine secretion from gut mucosa in inflammatory bowel disease.

Raithel M, Schneider HT, Hahn EG.

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BACKGROUND: Mast cell hyperplasia in the gut is a feature of inflammatory bowel disease (IBD), but the role of mast cells in this disease is still unclear. Since mast cell-nerve interactions might have some impact on intestinal inflammation, the present study investigated whether the neuropeptide substance P causes histamine secretion from human gut mucosal mast cells. METHODS: Four hundred and eighteen colorectal endoscopic samples from 20 patients with IBD and 10 controls were studied. Colorectal biopsy samples were cultured in an oxygenated medium for spontaneous histamine release or were stimulated with substance P, anti-human immunoglobulin E, and a combination of substance P and anti-human immunoglobulin E. Histamine release was measured using a highly sensitive and specific radioimmunoassay. RESULTS: Substance P failed to induce mast cell activation in histologically normal mucosa from controls. In contrast, mucosal specimens taken from inflamed IBD tissue or from uninvolved Crohn disease tissue showed a considerably enhanced rate of histamine secretion towards substance P, alone or in combination with anti-IgE. Unaffected mucosa with ulcerative colitis appeared insensitive towards substance P. CONCLUSIONS: The neuropeptide substance P was shown to preferentially enhance mucosal mast cell mediator secretion in active IBD. Thus, it appears likely that mast cell-nerve interactions are involved in as yet uninvestigated neurovegetative histamine-releasing processes of the gut in IBD.

PMID: 10423066 [PubMed - indexed for MEDLINE]

1: Brain Behav Immun. 1994 Sep;8(3):261-9.

ELSEVIER FULL-TEXT ARTICLE

Decreased beta-endorphin content in peripheral blood mononuclear leukocytes from patients with Crohn's disease.

Wiedermann CJ, Sacerdote P, Propst A, Propst T, Judmaier G, Kathrein H, Vogel W, Panerai AE.

Department of Internal Medicine, School of Medicine, University of Innsbruck, Austria.

Increased activation of lymphocytes in inflammatory bowel disease is reflected by alterations of various immunological functions including enhanced spontaneous secretion of rheumatoid factor by mononuclear cells. since in rheumatic diseases increased secretion of rheumatoid factor is associated with decreased levels of beta-endorphin in circulating blood mononuclear leukocytes, we investigated levels of leukocyte beta-endorphin in inflammatory bowel disease and compared them with those in hepatobiliary disorders and in healthy subjects. Levels of beta-endorphin were measured in extracts from peripheral blood mononuclear leukocytes by radioimmunoassay. beta-Endorphin levels ranged from 0 to 67 pg/10(6) cells. Mononuclear leukocytes from ulcerative colitis patients contained as much beta-endorphin as those from healthy control subjects. In patients with Crohn's disease, levels of beta-endorphin were reduced by as much as roughly 50%. An inverse relationship was found between leukocyte beta-endorphin on the one hand and erythrocyte sedimentation rate, blood granulocyte or thrombocyte counts, and C-reactive protein levels in plasma on the other. In patients with various hepatobiliary disorders including fatty liver disease, viral hepatitis, primary biliary cirrhosis, and cryptogenic or alcoholic cirrhosis, beta-endorphin levels were not significantly different from the normal range values. Data indicate that leukocyte beta-endorphin may be involved in regulation of the systemic inflammatory activity of Crohn's disease.

PMID: 7865897 [PubMed - indexed for MEDLINE]

1: Pathology. 1994 Jan;26(1):43-5.

Polycythemia vera and water-induced pruritus: evidence against mast cell involvement.

Buchanan JG, Ameratunga RV, Hawkins RC.

Department of Molecular Medicine, University of Auckland School of Medicine, New Zealand.

The mechanism of water-induced pruritus in patients with polycythemia vera is unknown. Evidence has been presented previously that bathing or showering may trigger mast cell degranulation and that release of a mediator by mast cells may be responsible for the pruritus. Tryptase is a specific marker of human mast cell secretory granules and its presence in body fluids indicates mast cell degranulation. In this study, serum tryptase levels were measured both before and one hour after showering in 11 patients suffering from polycythemia vera and water-induced pruritus. Tryptase was not found in the serum of any of the subjects one hour after showering, when levels would be expected to be near peak had significant mast cell degranulation occurred. These results argue against mass cell degranulation with systemic release of a mast cell product as the mechanism for water-induced pruritus in patients with polycythemia vera.

PMID: 8165024 [PubMed - indexed for MEDLINE]

1: Life Sci. 1993;53(18):1391-9.

Opiates, mast cells and histamine release.

Barke KE, Hough LB.

Department of Pharmacology and Toxicology, Albany Medical College, NY 12208.

Opiates have long been known to cause the release of histamine from mast cells, resulting in several undesirable effects, such as hypotension, urticaria, pruritis, and tachycardia. The mechanism of this opiate response has remained unclear, although it is known to be non-immunological in nature. A survey of the histamine-releasing properties of a variety of opiates shows that the pharmacology of opiate-induced histamine release from mast cells is distinct from that of known opiate receptors. Although functional opiate receptors may exist on mast cells and may be capable of modulating IgE-mediated histamine release, there is no evidence that these receptors account for opiate-induced histamine release. Since other basic compounds have been suggested to release histamine from mast cells by directly activating G-proteins, it seems possible that morphine and endogenous opiates may also share this mechanism.

Publication Types:

- Review
- Review, Tutorial

PMID: 7694026 [PubMed - indexed for MEDLINE]

1: Drug Dev Ind Pharm. 1999 May;25(5):591-6. Related Articles, Links

Macrophage depletion by albumin microencapsulated clodronate: attenuation of cytokine release in macrophage-dependent glomerulonephritis.

D'Souza MJ, Oettinger CW, Shah A, Tipping PG, Huang XR, Milton GV.

Department of Pharmaceutical Sciences, Southern College of Pharmacy, Mercer University, Atlanta, Georgia 30341, USA.

A macrophage plays an important role in mediating the inflammatory response. Cytokines released by activated macrophages contribute to inflammation in glomerulonephritis (GN). Clodronate, a biphosphonate, causes macrophage depletion when administered in an encapsulated form in liposomes. We used albumin as the polymer matrix to microencapsulate clodronate to the microspheres (MS) in the 1-micron size range. The purpose of this study was to (a) determine macrophage depletion by clodronate MS, (b) determine the effect of clodronate MS on endotoxin-induced cytokine release in vitro, and (c) assess the effect of clodronate MS on macrophage infiltration in experimental antiglomerular basement membrane nephritis. Macrophage depletion by clodronate MS was assessed by staining for the EDI marker. The results indicate greater than 95% depletion of macrophages from the spleen, liver, kidney, and blood. In the whole blood model, clodronate MS attenuated endotoxin-induced tumor necrosis factor alpha (TNF-alpha) and interleukin-1 beta (IL-1 beta) release, and the attenuation by the microencapsulated form of clodronate was also more effective than the free (solution) form of clodronate. Macrophage infiltration into the glomerulus in experimental GN was also blocked very effectively by pretreatment with clodronate MS. In conclusion, macrophage depletion by clodronate MS may be beneficial in reducing cytokine release and renal damage in GN.

PMID: 10219527 [PubMed - indexed for MEDLINE]

1: J Am Soc Nephrol. 1999 Jul;10(7):1506-15.

In vitro neutrophil activation by antibodies to proteinase 3 and myeloperoxidase from patients with crescentic glomerulonephritis.

Franssen CF, Huitema MG, Muller Kobold AC, Oost-Kort WW, Limburg PC, Tiebosch A, Stegeman CA, Kallenberg CG, Tervaert JW.

Department of Internal Medicine, University Hospital Groningen, The Netherlands. m.j.s.hraler@int.azh.nl

Previously, it was found that patients with necrotizing crescentic glomerulonephritis (NCGN) and anti-neutrophil cytoplasmic autoantibodies (ANCA) directed against proteinase 3 (anti-PR3) had a faster deterioration of renal function and more active renal vasculitic lesions than patients with ANCA directed against myeloperoxidase (anti-MPO). Because ANCA-mediated neutrophil activation is thought to play an important role in the pathophysiology of this form of glomerulonephritis, this study was conducted to determine whether anti-PR3 are capable of inducing a more pronounced activation of neutrophils in vitro than anti-MPO. To test this hypothesis, the release of reactive oxygen radicals, as assessed by ferricytochrome c reduction and by dihydrorhodamine 123 oxidation, and the release of granule constituents from healthy donor neutrophils upon stimulation with IgG fractions were measured from 17 anti-PR3- and 14 anti-MPO-positive patients with active NCGN. Patients with anti-PR3 had a higher renal activity index ($P < 0.05$) compared with patients with anti-MPO. IgG fractions from anti-PR3-positive patients induced more oxygen radical release from tumor necrosis factor-alpha-primed neutrophils compared with IgG fractions from anti-MPO-positive patients, as assessed by ferricytochrome c reduction ($P < 0.05$) and dihydrorhodamine 123 oxidation ($P < 0.01$). In addition, IgG fractions from anti-PR3-positive patients generated more neutrophil degranulation of beta-glucuronidase ($P < 0.01$) than IgG fractions from anti-MPO-positive patients. In conclusion, IgG fractions from anti-PR3-positive patients with NCGN are more potent activators of the respiratory burst and degranulation in vitro than IgG fractions from anti-MPO-positive patients. These observations may be relevant in view of the clinical differences between anti-PR3- and anti-MPO-positive patients with NCGN.

1: J Allergy Clin Immunol. 1999 Jun;103(6):1108-14. Related Articles, Links

J Allergy Clin Immunol

Murine mast cells exposed to mercuric chloride release granule-associated N-acetyl-beta-D-hexosaminidase and secrete IL-4 and TNF-alpha.

Dastych J, Walczak-Drzewiecka A, Wyczolkowska J, Metcalfe DD.

Department of Biogenic Amines, Polish Academy of Sciences, Lodz, Poland.

BACKGROUND: Mast cells, by virtue of their location within the skin, respiratory tract, and gastrointestinal system, are considered as potential targets for environmental agents with immunotoxic effects. Mercuric chloride (HgCl2), is a xenobiotic, which induces autoimmune glomerulonephritis and stimulates polyclonal IgE production. OBJECTIVE: We sought to determine the ability of HgCl2 to degranulate murine mast cells and promote cytokine secretion and whether this was an active biologic process. METHODS: Bone marrow-derived murine mast cells were exposed to HgCl2, and the release of N-acetyl-beta-D-hexosaminidase and secretion of IL-4 and TNF-alpha were measured. RESULTS: HgCl2 was found to directly activate murine mast cells to release the granule-associated enzyme N-acetyl-beta-D-hexosaminidase and to secrete the proinflammatory cytokines IL-4 and TNF-alpha. Cytokine secretion occurred hours after exposure to HgCl2 and required transcription and protein synthesis. The secretion of cytokines mediated by HgCl2 was additive to that which followed FcepsilonRI-induced mast cell activation. The IL-4 secretion by mast cells occurred at concentrations of HgCl2 (10(-6) mol/L to 10(-5) mol/L) comparable with those required to induce upregulation of IgE production in experimental animals. CONCLUSION: These findings demonstrate that HgCl2 will directly activate mast cells, which is followed by degranulation and IL-4 and TNF-alpha synthesis and secretion. These findings are consistent with recognition of HgCl2 as a biologically important environmentally derived immunotoxic agent for mast cells.

PMID: 10359893 [PubMed - indexed for MEDLINE]

All: 1 Review: 0

1: Anal Cell Pathol. 1998;16(3):141-50.

Comparative quantitative analysis of macrophage populations defined by CD68 and carbohydrate antigens in normal and pathologically altered human liver tissue.

Baldus SE, Zirbes TK, Weidner IC, Flucke U, Dittmar E, Thiele J, Dienes HP.

Institute of Pathology, University of Cologne, Germany.

Liver macrophages, which are involved in the different types of hepatitis, may indirectly induce hepatic fibrogenesis, since they have the possibility to activate hepatic stellate cells and fibroblasts by secretion of TGF-beta, TNF-alpha and IL-1. To evaluate variations of the number of liver macrophages and their subpopulations, a quantification was carried out in normal human liver tissue, fatty liver, fatty liver hepatitis and hepatitis B. Identification was performed by the mab PG-M1 (anti-CD68) and, comparatively, four lectins, Griffonia simplicifolia agglutinin I (GSA-I), Erythrina cristagalli agglutinin (ECA), peanut agglutinin (PNA) and soybean agglutinin (SBA). A slight decrease in the frequency of macrophages in pericentral fields was observable in fatty liver and fatty liver hepatitis as compared to normal liver tissue. On the other hand, the number of CD68+ cells was significantly enhanced in hepatitis B with moderate and severe inflammatory activity. The highest incidence of macrophages was found in portal tracts of liver with fatty liver hepatitis and, particularly, hepatitis B. The fraction of cells stained by ECA, PNA or SBA did not increase significantly under pathological conditions. In contrast, the percentage of GSA-I binding macrophages was higher in liver parenchyma of hepatitis B and in portal tract macrophages in fatty liver hepatitis and also hepatitis B. In conclusion, our results indicate that GSA-I may aid in the detection of the subpopulation of activated macrophages which are assumed to play a pivotal role in liver pathology.

PMID: 9699943 [PubMed - indexed for MEDLINE]

1: Am J Pathol. 1998 Feb;152(2):423-30.

Increased expression of monocyte chemotactic protein-1 during active hepatic fibrogenesis: correlation with monocyte infiltration.

Marra F, DeFranco R, Grappone C, Milani S, Pastacaldi S, Pinzani M, Romanelli RG, Laffi G, Gentilini P.

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Monocyte chemotactic protein (MCP)-1 is a chemoattractant and activator for circulating monocytes and T lymphocytes. We investigated MCP-1 protein and gene expression during chronic liver disease at different stages, using immunohistochemistry and in situ hybridization, respectively. In normal liver, a modest expression of MCP-1 was confined to few peri-sinusoidal cells and to bile duct epithelial cells. During chronic hepatitis, MCP-1 immunostaining and gene expression were evident in the inflammatory infiltrate of the portal tract. In tissue from patients with active cirrhosis, MCP-1 expression was clearly up-regulated and was present in the portal tract, in the epithelial cells of regenerating bile ducts, and in the active septa surrounding regenerating nodules. A combination of in situ hybridization for MCP-1 and immunohistochemistry showed that activated stellate cells and monocyte/macrophages contribute to MCP-1 expression in vivo together with bile duct epithelial cells. Comparison of serial sections of liver biopsies from patients with various degrees of necro-inflammatory activity showed that infiltration of the portal tracts with monocytes/macrophages is directly correlated with the expression of MCP-1. These data expand previous in vitro studies showing that secretion of MCP-1 may contribute to the formation and maintenance of the inflammatory infiltrate observed during chronic liver disease.

PMID: 9466568 [PubMed - indexed for MEDLINE]

1: Gut. 1999 Sep;45(3):416-20.

Serum concentrations and peripheral secretion of the beta chemokines monocyte chemoattractant protein 1 and macrophage inflammatory protein 1alpha in alcoholic liver disease.

Fisher NC, Neil DA, Williams A, Adams DH.

Liver Research Laboratories, MRC Centre for Immune Regulation, Institute of Clinical Science, Queen Elizabeth Medical Centre, Birmingham B15 2TH, UK.

BACKGROUND: Alcoholic liver disease is associated with increased hepatic expression of monocyte chemoattractant protein 1 (MCP-1) and macrophage inflammatory protein 1alpha (MIP-1alpha). AIMS: To determine whether concentrations of chemokines in the peripheral circulation reflect disease activity, and whether chemokine secretion is restricted to the liver or is part of a systemic inflammatory response in alcoholic liver disease. PATIENTS: Fifty one patients with alcoholic liver disease and 12 healthy controls. METHODS: Peripheral vein (and hepatic vein in patients undergoing transjugular liver biopsy) chemokine concentrations were measured by ELISA. Chemokine secretion and transcription in isolated peripheral mononuclear cells were assessed using ELISA and in situ hybridisation in patients with severe alcoholic hepatitis. RESULTS: Serum MCP-1 concentrations were higher in alcoholic hepatitis compared with cirrhosis or healthy controls. MIP-1alpha concentrations were below the assay sensitivity in most patients. Serum MCP-1 concentrations correlated significantly with serum aspartate aminotransferase and creatinine. In severe alcoholic hepatitis, MCP-1 concentrations were higher in hepatic compared with peripheral veins; in mild alcoholic hepatitis there was no difference. Mononuclear cell secretion of both MCP-1 and MIP-1alpha was higher in severe alcoholic hepatitis compared with healthy controls, and chemokine mRNA was identified in monocytes. CONCLUSIONS: Serum MCP-1 concentrations are raised in alcoholic liver disease and reflect severity of hepatic inflammation. Monocyte secretion of both MCP-1 and MIP-1alpha is increased in severe alcoholic hepatitis. Both intrahepatic sources and peripheral mononuclear cells contribute to the raised serum MCP-1 concentrations.

All: 1 Review: 1

1: Surg Clin North Am. 1999 Aug;79(4):699-710.

Etiopathogenesis of acute pancreatitis.

Karne S, Gorelick FS.

Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut, USA.

Acute pancreatitis is a disease that has many causes. Each cause seems to affect the acinar cell in some way that results in the premature activation and retention of potent proteolytic enzymes. These activated enzymes then injure the acinar cell and cause the immediate release of cytokines and activate the complement system. Together, these molecules attract and sequester inflammatory cells, in particular neutrophils, which causes further secretion of cytokines, free radicals, and other vasoactive molecules, such as nitric oxide. We propose that the released inflammatory molecules induce local effects, such as pancreatic edema and necrosis, and systemic complications, such as hypotension, tachycardia, fever, capillary leak syndrome, and hypoxia. The cytokines released in the pancreas also stimulate apoptosis, further enhancing the cell death response in pancreatitis. Much of the current research is aimed at understanding the links between these series of events and finding agents that can modulate the cascade of events involved in pancreatitis. What is promising in this endeavor is that the response produced with pancreatitis is nearly identical with all etiologies, suggesting that therapy may not have to be specific to a particular cause. The mechanistic models of AP presented herein are supported by preliminary clinical studies that suggest that protease and cytokine inhibitors may improve the course of AP in specific clinical settings.

Publication Types:
- Review
- Review, Tutorial

PMID: 10470320 [PubMed - indexed for MEDLINE]

1: Infect Immun. 1998 Nov;66(11):5357-63.

Helicobacter pylori lipopolysaccharide binds to CD14 and stimulates release of interleukin-8, epithelial neutrophil-activating peptide 78, and monocyte chemotactic protein 1 by human monocytes.

Bliss CM Jr, Golenbock DT, Keates S, Linevsky JK, Kelly CP.

Section of Gastroenterology, Boston Medical Center, Boston University School of Medicine, Boston, Massachusetts 02118, USA.

Helicobacter pylori gastritis is characterized by leukocyte infiltration of the gastric mucosa. The aims of this study were to determine whether H. pylori-derived factors stimulate chemokine release from human monocytes and to ascertain whether H. pylori lipopolysaccharide (LPS) may be responsible for this effect. Human peripheral blood monocytes were exposed to an H. pylori water extract (HPE) or to purified H. pylori LPS. Levels of the chemokines interleukin-8 (IL-8), epithelial neutrophil-activating peptide 78 (ENA-78), and monocyte chemotactic protein 1 (MCP-1) were measured by enzyme-linked immunosorbent assay. The contribution of H. pylori LPS to monocyte activation was determined by using the LPS antagonist Rhodobacter sphaeroides lipid A (RSLA) and a blocking monoclonal antibody to CD14 (60bca). HPE increased monocyte secretion of IL-8, ENA-78, and MCP-1. Heat treatment of HPE did not reduce its ability to activate monocytes. Purified H. pylori LPS also stimulated monocyte chemokine production but was 1,000-fold less potent than Salmonella minnesota lipid A. RSLA blocked H. pylori LPS-induced monocyte IL-8 release in a dose-dependent fashion (maximal inhibition 82%, $P < 0.001$). RSLA also inhibited HPE-induced IL-8 release (by 93%, $P < 0.001$). The anti-CD14 monoclonal antibody 60bca substantially inhibited IL-8 release from HPE-stimulated monocytes (by 88%, $P < 0.01$), whereas the nonblocking anti-CD14 monoclonal antibody did not. These experiments with potent and specific LPS inhibitors indicate that the main monocyte-stimulating factor in HPE is LPS. H. pylori LPS, acting through CD14, stimulates human monocytes to release the neutrophil-activating chemokines IL-8 and ENA-78 and the monocyte-activating chemokine MCP-1. Despite its low relative potency, H. pylori LPS may play an important role in the pathogenesis of H. pylori gastritis.

1: J Am Acad Dermatol. 1996 Aug;35(2 Pt 1):173-82. Related Articles, Links

Eosinophilic vasculitis in connective tissue disease.

Chen KR, Su WP, Pittelkow MR, Conn DL, George T, Leiferman KM.

Department of Dermatology, Mayo Clinic, Rochester, MN 55905, USA.

BACKGROUND: Neutrophilic and lymphocytic vascular inflammation is common in vasculitis associated with connective tissue disease (CTD). We recently identified eight patients with CTD and eosinophilic vasculitis. OBJECTIVE: The purpose of this study was to characterize a variant form of vasculitis in CTD with eosinophilic infiltration. METHODS: Of 98 CTD patients with cutaneous necrotizing vasculitis, eight were found with predominantly eosinophilic vascular infiltration. Nine CTD patients with cutaneous neutrophilic vasculitis were identified for comparison. Clinical and laboratory findings were reviewed and compared. Indirect immunofluorescence for eosinophil granule major basic protein (MBP), neutrophil elastase, and mast cell tryptase was performed on lesional tissue. MBP levels and eosinophil survival enhancing activity were assayed in sera from three patients. RESULTS: The patients with eosinophilic vasculitis had depressed serum complement levels and peripheral blood eosinophilia; MBP levels were elevated in serum and eosinophil survival was prolonged. Immunofluorescence of tissue showed marked angiocentric eosinophil MBP staining with peripheral neutrophil elastase staining; mast cell tryptase staining was notably absent. The patients with neutrophilic vasculitis were variably hypocomplementemic and did not have peripheral blood eosinophilia. Immunofluorescence showed marked angiocentric neutrophil elastase staining with scattered eosinophil MBP staining; mast cell tryptase staining showed normal mast cell numbers. CONCLUSION: Patients with eosinophilic vasculitis, CTD, and hypocomplementemia show vessel wall destruction in association with vessel wall deposition of cytotoxic eosinophil granule MBP, which suggests that eosinophils mediate vascular damage in this disease process. In addition, perivascular mast cells appear diminished, thereby suggesting that mast cell degranulation occurs.

PMID: 8708015 [PubMed - indexed for MEDLINE]

1: J Leukoc Biol. 1998 May;63(5):612-9.

Arterial and venular endothelial cell costimulation of cytokine secretion by human T cell clones.

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Vascular endothelial cell (EC) costimulation of cytokine secretion by T lymphocytes may be important in inflammation and allograft rejection. Venous and arterial iliac endothelial cells (VIEC, AIEC) both costimulate interleukin-2 (IL-2) production by peripheral blood lymphocytes (PBL) or T cell clones stimulated with phytohemagglutinin (PHA). Interferon-gamma (IFN-gamma) production is costimulated in a subset of clones but IL-4 is not. Surprisingly, two T cell clones were reciprocally better costimulated by VIEC or AIEC. EC activation by pretreatment with tumor necrosis factor alpha (TNF-alpha) does not increase T cell costimulation despite large increases in EC cell adhesion molecule expression. Neither VIEC nor AIEC express CTLA4-binding molecules and costimulation is blocked by cyclosporin A, suggesting that CD28 is not involved in EC costimulation of T cells. These data suggest that adult vascular EC costimulate production of IL-2 and IFN-gamma but not IL-4 by mature T cells, that EC costimulation is not increased in inflamed tissues, and that different EC optimally costimulate particular T cells. These findings have implications for the nature of the costimulatory signal(s) provided by EC and may be important in understanding vasculitis or atherosclerosis.

PMID: 9581806 [PubMed - indexed for MEDLINE]

1: Immunology. 1988 Aug;64(4):725-31.

Immunohistochemical detection of deposits of eosinophil-derived neurotoxin and eosinophil peroxidase in the myocardium of patients with Chagas' disease.

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An immunohistochemical study of eosinophil distribution in the inflammatory cell infiltrates of four different types of myocardial lesions associated with Chagas' disease--caused by Trypanosoma cruzi--showed larger numbers of these cells in areas presenting tissue necrosis and degeneration, most notably in patients with the most severe myocarditis from a histopathological stand-point. Using antisera specific for human eosinophil-derived neurotoxin or eosinophil peroxidase, we detected deposits of these secretion products on myofibres and in the interstitium of chagasic myocardium displaying necrosis and degeneration but rarely in other types of lesions. These deposits were not detectable in the myocardium of non-chagasic patients who had died from myocardial infarction (acute or in the scarring stage) or myocarditis secondary to bacterial endocarditis. When human eosinophil-derived neurotoxin was incubated with myoblast monolayers there was a significant cell injury, detachment and lysis. These effects were abrogated by yeast RNA, added as a competitive ribonuclease substrate, and inhibited by the ribonuclease inhibitor RNasin, suggesting that the ribonuclease activity of the eosinophil-derived neurotoxin was involved in the effect. These results suggest a link between eosinophil infiltration and necrosis in chagasic myocardial lesions and point to EDN, and perhaps other toxic eosinophil secretion products, as possible mediators of tissue damage.

PMID: 3049321 [PubMed - indexed for MEDLINE]

1: J Parasitol. 1989 Feb;75(1):129-33.

Eosinophil activation in acute and chronic chagasic myocardial lesions and deposition of toxic eosinophil granule proteins on heart myofibers.

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Cardiac lesions in patients with Chagas' disease are infiltrated with various types of inflammatory cells, including eosinophils (EOS). We determined the proportions of resting and activated EOS in 2 types of chagasic myocardial lesions to establish whether their presence correlated with lesion severity. One lesion type was defined by interstitial infiltration associated with degeneration and necrosis of myocardial fibers; the other type presented mild myocarditis but myofibers were preserved. In all cases (1 patient with acute and 5 patients with chronic Chagas' disease), a marked degree of EOS infiltration was seen in the necrotic areas after staining either with Giemsa or immunohistochemically, using antibodies specific for the EOS cationic protein or the major basic protein of the granule. In contrast, a very small number of EOS was present in areas of the very same tissue sections displaying mild myocarditis and preserved myofibers. Of the EOS present in the necrotic areas, 42-78% were in the activated secretory stage as evidenced immunohistochemically after incubation with a monoclonal antibody specific for an epitope of the secretory but not the storage form of the EOS cationic protein. In areas with mild myocarditis this proportion was much smaller, ranging from 9 to 28%. In all cases, both the total level of resting and activated EOS in the necrotic areas correlated well with the overall degree of severity of myocarditis evaluated histopathologically. Deposits of the major basic cationic proteins of the EOS granules were found on myofibers in the necrotic areas from the acute and chronic cases, indicating EOS degranulation.

PMID: 2918433 [PubMed - indexed for MEDLINE]

All: 1 Review: 0

1: J Pharmacol Exp Ther. 1999 Mar;288(3):1349-56.

Potent mast cell degranulation and vascular permeability triggered by urocortin through activation of corticotropin-releasing hormone receptors.

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Urocortin (Ucn) is related to corticotropin-releasing hormone (CRH), and both are released in the brain under stress where they stimulate CRH 1 and 2 receptors (CRHR). Outside the brain, they may have proinflammatory actions through activation of mast cells, which are located perivascularly close to nerve endings and degranulate in response to acute psychological stress. Here, we report that a concentration of intradermal Ucn as low as 10 nM induced dose-dependent rat skin mast cell degranulation and increased vascular permeability. This effect appeared to be equipotent to that of calcitonin gene-related peptide and neurotensin. Ucn-induced skin vasodilation was inhibited by pretreatment with the mast cell stabilizer disodium cromoglycate (cromolyn) and was absent in the mast cell-deficient W/Wv mice. The selective nonpeptide CRH receptor 1 antagonist, antalarmin and the nonselective peptide antagonist astressin both reduced vascular permeability triggered by Ucn but not that by Substance P or histamine. In contrast, the peptide antagonist alpha-helical CRH-(9-41) reduced the effect of all three. The vasodilatory effect of Ucn was largely inhibited by pretreatment with H1 receptor antagonists, suggesting that histamine is the major mediator involved in vitro. Neuropeptide depletion of sensory neurons, treatment with the ganglionic blocker hexamethonium, or in situ skin infiltration with the local anesthetic lidocaine did not affect Ucn-induced vascular permeability, indicating that its in situ effect was not mediated through the peripheral nervous system. These results indicate that Ucn is one of the most potent triggers of rat mast cell degranulation and skin vascular permeability. This effect of Ucn may explain stress-induced disorders, such as atopic dermatitis or psoriasis, and may lead to new forms of treatment.

1: Brain Behav Immun. 1999 Sep;13(3):225-39.

ELSEVIER FULLSTEXT ARTICLE

Acute immobilization stress triggers skin mast cell degranulation via corticotropin releasing hormone, neurotensin, and substance P: A link to neurogenic skin disorders.

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Many skin disorders, such as atopic dermatitis and psoriasis, worsen during stress and are associated with increased numbers and activation of mast cells which release vasoactive, nociceptive, and proinflammatory mediators. Nontraumatic acute psychological stress by immobilization has been shown to induce mast cell degranulation in the rat dura and colon. Moreover, intradermal injection of corticotropin-releasing hormone (CRH) or its analogue urocortin (10(-5)-10(-7) M) induced skin mast cell degranulation and increased vascular permeability. Here, we investigated the effect of acute immobilization stress on skin mast cell degranulation by light microscopy and electron microscopy. Immobilization for 30 min resulted ($P < 0.05$) in degranulation of 40.7 +/- 9.1% of skin mast cells compared to 22.2 +/- 7.3% in controls killed by CO(2) or 17.8 +/- 2.4% in controls killed by pentobarbital. Pretreatment intraperitoneally (ip) with antiserum to CRH for 60 min prior to stress reduced ($P < 0.05$) skin mast cell degranulation to 21.0 +/- 3. 3%. Pretreatment with the neurotensin (NT) receptor antagonist SR48692 reduced ($P < 0.05$) mast cell degranulation to 12.5 +/- 3.4%, which was significantly ($P < 0.05$) below control levels. In animals treated neonatally with capsaicin to deplete their sensory neurons of their neuropeptides, such as substance P (SP), mast cell degranulation due to immobilization stress was reduced to about 15%. This is the first time that stress has been shown to trigger skin mast cell degranulation, an action not only dependent on CRH, but apparently also involving NT and SP. These findings may have implications for the pathophysiology and possible therapy of neuroinflammatory skin disorders such as atopic dermatitis, neurogenic pruritus, or psoriasis, which are induced or exacerbated by stress.

1: Endocrinology. 1998 Jan;139(1):403-13.

Corticotropin-releasing hormone induces skin mast cell degranulation and increased vascular permeability, a possible explanation for its proinflammatory effects.

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Mast cells are involved in atopic disorders, often exacerbated by stress, and are located perivascularly close to sympathetic and sensory nerve endings. Mast cells are activated by electrical nerve stimulation and millimolar concentrations of neuropeptides, such as substance P (SP). Moreover, acute psychological stress induces CRH-dependent mast cell degranulation. Intradermal administration of rat/human CRH (0.1-10 microM) in the rat induced mast cell degranulation and increased capillary permeability in a dose-dependent fashion. The effect of CRH on Evans blue extravasation was stronger than equimolar concentrations of the mast cell secretagogue compound 48/80 or SP. The free acid analog of CRH, which does not interact with its receptors (CRHR), had no biological activity. Moreover, systemic administration of antalarmin, a nonpeptide CRHR1 antagonist, prevented vascular permeability only by CRH and not by compound 48/80 or SP. CRHR1 was also identified in cultured leukemic human mast cells using RT-PCR. The stimulatory effect of CRH, like that of compound 48/80 on skin vasodilation, could not be elicited in the mast cell deficient W/Wv mice but was present in their +/+ controls, as well as in C57BL/6J mice; histamine could still induce vasodilation in the W/Wv mice. Treatment of rats neonatally with capsaicin had no effect on either Evans blue extravasation or mast cell degranulation, indicating that the effect of exogenous CRH in the skin was not secondary to or dependent on the release of neuropeptides from sensory nerve endings. The effect of CRH on Evans blue extravasation and mast cell degranulation was inhibited by the mast cell stabilizer disodium cromoglycate (cromolyn), but not by the antisecretory molecule somatostatin. To investigate which vasodilatory molecules might be involved in the increase in vascular permeability, the CRH injection site was pretreated with the H1-receptor antagonist

diphenhydramine, which largely inhibited the CRH effect, suggesting that histamine was involved in the CRH-induced vasodilation. The possibility that nitric oxide might also be involved was tested using pretreatment with a nitric oxide synthase inhibitor that, however, increased the effect of CRH. These findings indicate that CRH activates skin mast cells at least via a CRHR1-dependent mechanism leading to vasodilation and increased vascular permeability. The present results have implications for the pathophysiology and possible therapy of skin disorders, such as atopic dermatitis, eczema, psoriasis, and urticaria, which are exacerbated or precipitated by stress.

PMID: 9421440 [PubMed - indexed for MEDLINE]

1: Acta Derm Venereol Suppl (Stockh). 1989;144:70-7. Related Articles, Links

Histamine and atopic eczema.

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Apart from increased production of immunoglobulin E antibodies and disturbed T-cell regulation, altered patterns of releasability of vasoactive mediators have been described in patients with atopic eczema. The best studied substance is histamine which is a classical inducer of pruritus in man. Elevated concentrations of histamine have been found in vivo in the skin and in the plasma of patients with atopic eczema especially during exacerbation of the disease. Similar findings have been described for other atopic diseases as extrinsic bronchial asthma. Histamine acts via characteristic receptors; symptoms as itch, wheal formation, mucus production, contraction of smooth muscle, tachycardia H2-effects include acid secretion in the stomach as well as the development of flush and itch reactions, blood pressure changes and cardiac arrhythmia. Of special interest is an inhibitory effect of histamine on lymphocyte reactions mediated via a H2-receptor. The existence of a new H3-receptor in the brain serving as autocrine feed-back inhibitor of histaminergic neurones has been established in the rat but not yet in man. In vitro an increased histamine releasability of peripheral leukocytes has been found after stimulation with a variety of different substances. The difference between patients with atopic eczema and normals is generally most pronounced after stimulation with anti-IgE. There is, however, a tendency towards an increased spontaneous histamine release compared to normals. The release reaction of histamine seems to occur more rapidly in atopics compared to normals.(ABSTRACT TRUNCATED AT 250 WORDS)

Publication Types:

- Review
- Review, Tutorial

PMID: 2477978 [PubMed - indexed for MEDLINE]

1: Nord Med. 1995;110(3):79-81.

[Cytokines and skin diseases]

[Article in Danish]

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Many skin diseases such as eczema and psoriasis are characterised by a chronic inflammatory skin condition. In this respect they resemble other chronic diseases such as rheumatoid arthritis, bronchial asthma, ulcerous colitis and Crohn's disease. A persistent accumulation, predominantly of T-lymphocytes constitutes the central pathophysiological feature of such diseases. The past 15-20 years have witnessed the characterisation of an extensive series of peptides known as cytokines. These are soluble, relatively low molecular weight peptides which at low concentrations mediate regulation of cellular receptors, new phenotype expression, secretion and migration. Many cytokines have been found to be present in conjunction with skin diseases, and it is suggested that they are involved in the development of inflammation.

PMID: 7892122 [PubMed - indexed for MEDLINE]

1: Cancer Res. 1989 Sep 15;49(18):5066-72. Related Articles, Links

Effects of irradiation on the release of growth factors from cultured bovine, porcine, and human endothelial cells.

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The effects of radiation on the release of mitogenic factors into the media of cultured endothelial cells of bovine, porcine, and human origins were studied. Although unirradiated controls revealed a significant background activity, single doses of irradiation (20-60 Gy) resulted in a dose-related increased release of growth factor activity, measured by the mitogenic effects of the conditioned media on both 3T3 mouse fibroblasts and unirradiated endothelial cells serving as target cells. Receptor binding competition assays for the platelet-derived growth factor receptor revealed that 12-28% of the total mitogenic activity was due to platelet-derived growth factor-like mitogens. Mitogenic assays using endothelial cells and specific antibody mediated inhibition assays suggested that another component of the mitogenic activity was due to a fibroblast growth factor-like factor. Although radiation resulted in a significant increase in cell death, the enhanced growth factor activities did not appear to result from cell lysis-related leakage of intracellular stores of growth factor. Instead, our data suggest that the growth factors were synthesized de novo and secreted at elevated levels by the cells which maintained postradiation a high level of metabolic activity. Time course studies demonstrated that the growth factors accumulation in the conditioned media started within the first 24 h after radiation and reached a plateau within 72 h after treatment. Radiation-induced release of endothelial cell-derived growth factors may be involved in the pathogenesis of both early vascular damage and the late fibrosis which represents a prominent feature of late radiation damage in normal tissues.

PMID: 2548709 [PubMed - indexed for MEDLINE]

1: Radiat Res. 1993 Oct;136(1):37-41. Related Articles, Links

Release of interleukin-1 by human alveolar macrophages after in vitro irradiation.

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Therapeutic thoracic irradiation may induce two late pulmonary injury syndromes: radiation pneumonitis and subsequent pulmonary fibrosis. The alveolar macrophage has been considered a radioresistant cell and not a target cell involved in the pathogenesis of either type of radiation-induced lung injury. Alveolar macrophage-derived cytokines, including interleukin-1 (IL-1) and tumor necrosis factor (TNF), have been demonstrated to participate in inflammatory and fibrotic responses in the lung after various other types of lung injury. To evaluate whether the release of cytokines by alveolar macrophages is induced by radiation doses used clinically, alveolar macrophages recovered from nonsmoking volunteers were exposed in vitro to a single dose of 2 Gy and then maintained in culture for 18 h. Culture supernatants and cell lysates were then recovered and analyzed for IL-1 alpha and IL-1 beta by radioimmunoassay. Supernatants of irradiated alveolar macrophages contained significantly increased amounts of IL-1 alpha ($P < 0.04$) and IL-1 beta ($P < 0.02$) as well as total IL-1 (IL-1 alpha and IL-1 beta) ($P < 0.02$) compared to nonirradiated alveolar macrophages. Cell lysates of irradiated alveolar macrophages also contained increased amounts of IL-1 alpha and IL-1 beta, although differences from controls were not significant. The finding of increased release of IL-1 by alveolar macrophages after exposure to a single, clinically relevant dose of radiation suggests that the function of human alveolar macrophages is likely altered during therapeutic use of thoracic irradiation. Whether this release of IL-1 by alveolar macrophages contributes to early lung inflammation induced by thoracic irradiation is unclear.

PMID: 8210336 [PubMed - indexed for MEDLINE]

1: Am J Physiol Lung Cell Mol Physiol. 2002 Jul;283 (1):L1-11.

Metalloproteinase and growth factor interactions: do they play a role in pulmonary fibrosis?

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Chronic lung disease due to interstitial fibrosis can be a consequence of acute lung injury and inflammation. The inflammatory response is mediated through the migration of inflammatory cells, actions of proinflammatory cytokines, and the secretion of matrix-degrading proteinases. After the initial inflammatory insult, successful healing of the lung may occur, or alternatively, dysregulated tissue repair can result in scarring and fibrosis. On the basis of recent insights into the mechanisms underlying acute lung injury and its long-term consequences, data suggest that proteinases, such as the matrix metalloproteinases (MMPs), may not only be involved in the breakdown and remodeling that occurs during the injury but may also cause the release of growth factors and cytokines known to influence growth and differentiation of target cells within the lung. Through the release of and activation of fibrosis-promoting cytokines and growth factors such as transforming growth factor-beta1, tumor necrosis factor-alpha, and insulin-like growth factors by MMPs, we propose that these metalloproteinases may be integral to the initiation and progression of pulmonary fibrosis.

Publication Types:
- Review

PMID: 12060555 [PubMed - indexed for MEDLINE]

1: J Toxicol Environ Health A. 1999 Jun 25;57(4):247-66.

Use of tetrandrine to differentiate between mechanisms involved in silica-versus bleomycin-induced fibrosis.

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Animals exposed to silica or bleomycin (BLM) develop pulmonary fibrosis. Tetrandrine (TT) has been shown to inhibit stimulant-induced macrophage respiratory burst and effectively reduce silica-induced lung injury. The present study employed TT as a probe to assess the differences in mechanisms involved in silica- and BLM-induced pulmonary responses. Rats received a single intratracheal instillation of silica (40 mg/rat, sacrificed 4 wk postexposure) or BLM (1 mg/kg or approximately 0.25 mg/rat, sacrificed up to 2 wk postexposure). TT was administered orally at 18 mg/kg, 3 times/wk for desired time periods beginning 5 d before silica or BLM exposure. Both the silica and BLM exposures resulted in a significant increase in lung weight, total protein, lactate dehydrogenase (LDH), and phospholipids (PL) content in the acellular fluid from the first lavage, and hydroxyproline content in the lung tissue. Alveolar macrophages (AM) isolated from rats exposed to silica or BLM exhibited significant increases in secretion of interleukin-1 (IL-1), tumor necrosis factor alpha (TNF-alpha), and transforming growth factor beta (TGF-beta). TT treatment significantly lowered the silica- or BLM-induced increase in lung weight, while marginally reducing the release of IL-1 and TNF-alpha by AM. TT, however, markedly inhibited the silica-induced increase in the acellular protein, LDH and PL, hydroxyproline content, and the production of TGF-beta by AM but had no marked effect on these same parameters in BLM-exposed rats. Histological examination of rats exposed to BLM for 14 d showed pulmonary inflammation and fibrosis. TT treatment had only a small effect on limiting the extent of these lesions and did not significantly affect their severity. In summary, data indicate that many inflammatory and fibrotic effects of in vivo silica exposure are substantially attenuated by TT, whereas the stimulation by BLM is only marginally affected by this drug. Since TT acts to attenuate AM-mediated reactions, these results suggest that AM may play a pivotal role in silica-induced fibrotic development and may be less involved in the